CASE REPORT

Paraneoplastic cerebellar degeneration in a patient with anaplastic non-Hodgkin's lymphoma

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SUMMARY

A 31-year-old man presented with a subacute cerebellar syndrome of unknown aetiology. Investigations including a paraneoplastic antibody screen were negative and a working diagnosis of possible vasculitis was concluded. After 1 month, he re-presented with worsening of his symptoms and a neck lump. He was diagnosed with anaplastic lymphoma kinase, negative non-Hodgkin's lymphoma and paraneoplastic cerebellar syndrome. A more extensive paraneoplastic antibody screen found patient to be Tr (delta/notch-like epidermal growth factor-related receptor) antibody positive. After a period of chemotherapy and steroid treatments, his symptoms are now stable in terms of cerebellar function. This case report summarises a very rare diagnosis of paraneoplastic cerebellar degeneration with a positive onconeural antibody associated with anaplastic non-Hodgkin's lymphoma.

BACKGROUND

Paraneoplastic neurological syndromes are rare immune-mediated phenomena which can affect both the central and the peripheral nervous system.¹ Over recent times, categorisation of these syndromes according to primary disease and antibody associations has led to both diagnostic and therapeutic interest. Paraneoplastic cerebellar degeneration (PCD) is a well-known syndrome associated with anti-Hu, anti-Yo and Tr (delta/notch-like epidermal growth factor-related receptor (DNER)) antibodies.² We present a rare case whereby a patient presents with non-Hodgkin's lymphoma (NHL) and PCD with Tr (DNER) antibody association. By describing this in our case report, we aim to provide further evidence for clinicians, including neurologists, haematologists and general physicians, and highlight the need to consider rarer causes to reach a prompt diagnosis.

CASE PRESENTATION

A 31-year-old man who worked as a personal trainer based in Abu Dhabi presented with a short 3-week history of slurred speech, vertigo and gait disturbances. He did not have any other systemic symptoms and medical history included eosinophilic oesophagitis and eczema. He had recently travelled to Italy and Thailand on holiday and has multiple food allergies. There was no significant family history and denied any substance misuse.

On examination, he was found to have dysarthria, dysdiadochokinesis, positive Romberg's sign

and an ataxic gait. His general, neurological and cognitive examination otherwise was normal.

His presentation was pointing towards a cerebellar syndrome and he underwent extensive diagnostic workup. MRI of the brain and spine, identified multiple supratentorial white matter fluid attenuated and inversion recovery (FLAIR) hyperintensities, however, no evidence of active disease (see figure 1). Differential diagnosis at this stage included a vasculitic and/or inflammatory process. CT of the chest, abdomen and pelvis was normal.

Initial haematological, biochemical, autoimmune, microbiological and cerebrospinal fluid (CSF) investigations were normal. However, he was found to have positive oligoclonal bands on his CSF which along with the imaging evidence contributed to the working diagnosis.

He was treated with intravenous steroids and had a favourable recovery. One month later he re-presented with worsening of his cerebellar symptoms and with a neck lump. This firm swelling in the posterior triangle of neck was found to be lymph node and a biopsy was performed. This identified an anaplastic lymphoma kinase (ALK) negative NHL. Immunohistochemistry showed strong positive staining of large cells with CD30. Furthermore, molecular cytogenetic analysis did not show evidence of DUSP22 rearrangement. This further consolidated diagnosis of ALK-negative anaplastic large cell lymphoma. A nuclear medicine scan showed uptake of fluorodeoxyglucose in the neck (see figure 2) and periportal lymph nodes. Bone marrow biopsy did not show any infiltration. He was thereafter commenced on three cycles of cyclophosphamide, doxorubicin, vincristine, prednisolone chemotherapy. He was also given a trial of intravenous immunoglobulins for his cerebellar symptoms with no benefit. It was felt that his cerebellar symptoms were secondary to a paraneoplastic syndrome.

Despite improvement in terms of his NHL, his cerebellar symptoms over the following 3 months became progressively worse to the point he required significant amount of assistance in activities of daily living. At this stage, alternative aetiologies such as central nervous system (CNS) lymphoma were considered for his cerebellar problems. A repeat MRI of the brain showed cerebellar atrophy and no evidence of CNS lymphoma.

A more extensive paraneoplastic antibody screen was sent. The patient was found to be positive for Tr (DNER) antibody, a well-characterised marker of PCD associated with lymphoma. The definitive

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Figure 1 MRI head sagittal view. This demonstrates abnormally numerous white matter hyperintensities in the supratentorial parenchyma (superior green arrow) and cerebellar atrophy for age (inferior green arrow).

diagnosis of PCD was made after roughly 5 months of onset of symptoms. This was based on the clinical history, antibody association and exclusion of other causes.

OUTCOME AND FOLLOW-UP

Only supportive treatments were trialed for his cerebellar problems with the hope that he would get better with the treatment of the underlying NHL. His cerebellar symptoms have stabilised on monthly follow-up; however, a poor prognosis is predicted in relation to the NHL.

Figure 2 Whole body 18F fluorodeoxyglucose (FDG) positron emission tomography/CT scan. This image demonstrates a right level II neck lymph node with high-grade FDG uptake.

DISCUSSION

Paraneoplastic neurological syndromes are due to remote effects of cancer on nervous system unrelated to direct or metastatic mechanism of disease spread. It is commonly due to autoimmune phenomena whereby antigens on neurological cells are also present by the primary tumour.^{1,2} In the case described above, the cerebellar syndrome was the first presentation with the diagnosis of NHL made roughly 6 weeks later. PCD is a well-described syndrome that leads to severe disability, often associated with gynaecological, lung and Hodgkin's lymphoma (HL).³ It is very rarely associated with NHL; however, there has been a very small number of cases reported.⁴ A recent analysis of 24 PCD cases associated with lymphoma identified two-thirds of cases being HL, while the remaining NHL.³ Prevalence of peripheral nervous system (eg, demyelinating polyradiculopathies) and motor neuron involvement was much higher in NHL.^{3,4}

Diagnosis of a PND can be classified as 'possible' or 'definite'. In the case discussed due to a presence of classical syndrome and presence of a cancer the likelihood is 'definite' (if other causes are excluded). Positive onconeural antibodies are not essential as only up to a quarter of patients do not have a positive antibody association.¹⁻³

In the case of PCD, it has been postulated that the Purkinje cells in the cerebellum and the T lymphocytes share antigenic surface markers.^{5,6} However, the association has been strongest with HL and PCD. Immunological studies have shown strong association between Tr (DNER) antibody, HL and PCD with quite high specificity.⁷ This makes the association with NHL as in the case discussed very unusual and rare. Due to this unusual association, close examination of the pathology specimens was carried out. Immunohistochemical and molecular cytogenetic testing found no evidence to alter the diagnosis of ALK-negative anaplastic large cell lymphoma in this case report. Other antibodies associated with PCD include anti-Yo, anti-bGluR1, anti-Ri and anti-Hu; however, they do not associate with HL or NHL to the extent of Tr (DNER) antibody.^{4,8}

In terms of neurological outcomes, 50% of patients with HL and PCD responded to chemotherapy (with or without immunosuppression) whereas only twenty-four percent in patients with PCD and NHL.³ Diagnosis of PCD did not dramatically effect mortality in these patients however they had significant morbidity burden.^{9,10} Alternative therapies have not been reported in the literature and future research efforts should be directed at dampening the effects of the neurological syndrome.

Learning points

- ▶ Paraneoplastic cerebellar degeneration is rare disorder, even rarer in cases of non-Hodgkin's lymphoma, and is most commonly associated with the Tr (delta/notch-like epidermal growth factor-related receptor) antibody in Hodgkin's lymphoma and non-Hodgkin's lymphoma.
- ▶ After exclusion of other potential causes of cerebellar syndrome, a paraneoplastic syndrome should be suspected and investigated appropriately.
- ▶ Treatment options currently are limited to curing the underlying cancer and supportive measures.

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